

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A substantially pure preparation of a plasmin inhibitor characterised in that it is a single stage competitive inhibitor of plasmin, **wherein "substantially pure" means that at least 60% of the total material in the preparation is the plasmin inhibitor.**
2. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1 \times 10^{-8} \text{ M}^{-1}$ to $1 \times 10^{-10} \text{ M}^{-1}$.
3. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $5 \times 10^{-8} \text{ M}^{-1}$ to $8 \times 10^{-9} \text{ M}^{-1}$.
4. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1 \times 10^{-9} \text{ M}^{-1}$ to $5 \times 10^{-9} \text{ M}^{-1}$.
5. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $4 \times 10^{-5} \text{ sec}^{-1} \text{ M}^{-1}$ to $5 \times 10^{-7} \text{ sec}^{-1} \text{ M}^{-1}$.
6. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $1 \times 10^{-6} \text{ sec}^{-1} \text{ M}^{-1}$ to $1 \times 10^{-7} \text{ sec}^{-1} \text{ M}^{-1}$.
7. (Original) The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $2 \times 10^{-6} \text{ sec}^{-1} \text{ M}^{-1}$ to $9 \times 10^{-6} \text{ sec}^{-1} \text{ M}^{-1}$.

8. (Currently Amended) The plasmin inhibitor of claim 1 comprising a polypeptide selected from the group consisting of:

- (a) Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-[[Ph]] Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:2];
- (b) Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:4];
- (c) Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:6];
- (d) Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:8];
- (e) Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:10]; **and**
- (f) Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:12][[;]]
- (g) ~~a biologically active fragment of any one of SEQ ID NO:2, 4, 6, 8, 10 and 12; and~~
- (h) ~~a variant or derivative of any of the foregoing polypeptides or fragments thereof.~~

9. (Currently amended) The plasmin inhibitor of claim [[8]]1, ~~wherein said variant has comprising a polypeptide having~~ the general formula:

KDZPZ~~Y~~CZLBBZBGXCXXXBXF~~A~~YXB~~ZZZ~~CBZFBYGGCXBNANNFXTXEECESTC

AA (I), wherein:

- X is any amino acid;
- Y is a hydrophobic amino acid;
- A is an aromatic amino acid;
- Z is K, R, H, D, E, Q or N; and

B is a neutral amino acid, or P, A, G, S, T, V or L.

10. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 3 is H or R.
11. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 5 is K, N, E or D.
12. (Original) The plasmin inhibitor of claim 9, wherein the \tilde{Y} at position 6 is F or L.
13. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 8 is E or K.
14. (Original) The plasmin inhibitor of claim 9, wherein the B at position 10 is P or L.
15. (Original) The plasmin inhibitor of claim 9, wherein the B at position 11 is P or A.
16. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 12 is E or D.
17. (Original) The plasmin inhibitor of claim 9, wherein the B at position 13 is T or I.
18. (Original) The plasmin inhibitor of claim 9, wherein the X at position 15 is P, S or R.
19. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 17 is K, N, E, D or R.
20. (Original) The plasmin inhibitor of claim 9, wherein the X at position 18 is D, G, A or V.
21. (Original) The plasmin inhibitor of claim 9, wherein the X at position 19 is F, N, K or R.
22. (Original) The plasmin inhibitor of claim 9, wherein the X at position 20 is T, P, F or I.
23. (Original) The plasmin inhibitor of claim 9, wherein the B at position 21 is G, V or P.
24. (Original) The plasmin inhibitor of claim 9, wherein the X at position 22 is A, S or R.
25. (Original) The plasmin inhibitor of claim 9, wherein the \tilde{A} at position 24 is Y or H.
26. (Original) The plasmin inhibitor of claim 9, wherein the X at position 26 is S or N.

27. (Original) The plasmin inhibitor of claim 9, wherein the B at position 27 is P, A or T.
28. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 28 may be D or R.
29. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 29 is E, D, H or Q.
30. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 30 is H, K, R or Q.
31. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 31 is K, Q or E.
32. (Original) The plasmin inhibitor of claim 9, wherein the B at position 33 is L or I.
33. (Original) The plasmin inhibitor of claim 9, wherein the Z at position 34 is E or K.
34. (Original) The plasmin inhibitor of claim 9, wherein the B at position 36 is L or I.
35. (Original) The plasmin inhibitor of claim 9, wherein the X at position 41 is E, G or K.
36. (Original) The plasmin inhibitor of claim 9, wherein the B at position 42 is C or G.
37. (Original) The plasmin inhibitor of claim 9, wherein the X at position 48 is K, N or I.
38. (Original) The plasmin inhibitor of claim 9, wherein the X at position 50 is K, Q or I.
39. (Currently Amended) The plasmin inhibitor of claim 8 or claim 9, wherein the polypeptide comprises a leader peptide comprising the sequence:- Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:16]; ~~, or a biologically active fragment thereof, or variant or derivative of these.~~
40. (Original) The plasmin inhibitor of claim 39, wherein the polypeptide is selected from the group consisting of:-
 - (a) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:16];
 - (b) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-

Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:18];

- (c) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:20];
- (d) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:22];
- (e) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:24]; and
- (f) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:26].

41. (Withdrawn) An isolated polynucleotide encoding the polypeptide of claim 8.

42. (Withdrawn) An isolated polynucleotide selected from the group consisting of:

- (a) AAGGACCGTCCGGATTCTGTGAAC TG C CT GCT GAC ACCGGACCATGTAGA GTCAGATTCCCATCCTTCACTACAACCCAGATGAAAAAAAGTGCTAGAGT TTATTTATGGTGGATGCGAAGGGAAATGCTAACAAATTATCACCAAAGAGG AATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:1];
- (b) AAGGACCGTCCAGAGTTGTGAAC TG C CT GCT GAC ACCGGACCATGTAGA GTCAGATTCCCATCCTTCACTACAACCCAGATGAAACAAAAATGCCTAGAG TTTATTTATGGTGGATGCGAAGGGAAATGCTAACAAATTATCACCAAAGAG GAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:3];
- (c) AAGGACCGTCCAAATTCTGTAAACTG C CT GCT GAAACCGGACGATGTAAT G C CAAAATCCCACGCTTCACTACAACCCACGTCAACATCAATGCATAGAG TTTCTCTATGGTGGATGCGGAGGGAAATGCTAACAAATTAAAGACCATTAAG GAATGCGAAAGCACCTGTGCTGCATGA [SEQ ID NO:5];
- (d) AAGGACCATCCAAAATTCTGTGAAC TG C CT GCT GAAACCGGATCATGTAAA GGCAACGTCCCACGCTTCACTACAACGCAGATCATCATCAATGCCTAAAA

TTTATTATGGTGGATGTGGAGGGAAATGCTAACAAATTAAAGACCATAGAG
GAAGGCAAAAGCACCTGTGCTGCCTGA [SEQ ID NO:7];

- (e) AAGGACCGTCCAAAATTCTGTGAAC TGCTCCTGACACCGGATCATGTGAA
GACTTACCGGAGCCTCACTACAGCACACGTGATCGTAATGCATAGAG
TTTATTATGGTGGATGCGGAGGGAAATGCTAACAAATTATCACCAAAGAG
GAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:9];
- (f) AAGGACCGTCCAAAGTTCTGTGAAC TGCTGCTGACATCGGACCATGGGAT
GACTTACCGGAGCCTCACTACAGCCCACGTGAAACATGAATGCATAGAG
TTTATTATGGTGGATGCAAAGGGAAATGCTAACAAACTTAATACCCAAGAG
CAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:11];
- (g) a biologically-active polynucleotide fragment of any one of SEQ ID NOS 1, 3, 5, 7, 9, 11, 12, 14, 16, 18 and 20; and
- (h) a polynucleotide homologue of any of the foregoing sequences.

43. (Withdrawn) The polynucleotide of claim 42 further comprising a nucleotide sequence encoding a leader peptide.

44. (Withdrawn) The polynucleotide of claim 43, wherein the nucleotide sequence comprises the sequence:-

ATGTCTTCTGGAGGTCTTCTCTCCTGCTGGGACTCCTCACCCCTCTGGG
AGGTGCTGACCCCCGTCTCCAGC [SEQ ID NO:13] or a biologically active fragment thereof, or a polynucleotide homologue of these.

45. (Withdrawn) The polynucleotide of claim 43, wherein said polynucleotide is selected from the group consisting of:

- (a) ATGTCTTCTGGAGGTCTTCTCTCCTGCTGGGACTCCTCACCCCTCTGGGAGG
TGCTGACCCCCGTCTCCAGCAAGGACCGTCCGGATTCTGTGAAC TGCTC
TGACACCGGACCATGTAGAGTCAGATTCCCATCCTTCTACTACAACCCAGA
TGAAAAAAAAGTGCCTAGAGTTATTATGGTGGATGCGAAGGGAAATGCTAA
CAATTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:15];
- (b) ATGTCTTCTGGAGGTCTTCTCTCCTGCTGGGACTCCTCACCCCTCTGGGAGG
TGCTGACCCCCGTCTCCAGCAAGGACCGTCCAGAGTTGTGTGAAC TGCTC
CTGACACCGGACCATGTAGAGTCAGATTCCCATCCTTCTACTACAACCCAG
ATGAACAAAAATGCCTAGAGTTATTATGGTGGATGCGAAGGGAAATGCTA
ACAATTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:17];

- (c) ATGTCTTCTGGAGGTCTTCTCCTGCTGGACTCCTCACCCCTCTGGGAGG TGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAATTCTGTAAACTGCCTGC TGAAACCGGACGATGTAATGCCAAATCCCACGCTTACTACAACCCACG TCAACATCAATGCATAGAGTTCTATGGTGGATGCGGGAGGGAAATGCTAA CAATTAAAGACCATTAAGGAATGCGAAAGCACCTGTGCTGCATGA [SEQ ID NO:19];
- (d) ATGTCTTCTGGAGGTCTTCTCCTGCTGGACTCCTCACCCCTCTGGGAGG TGCTGACCCCCGTCTCCAGCAAGGACCATCCAAATTCTGTAACTCCCTGC TGAAACCGGATCATGTAAGGCAACGTCCCACGCTTACTACAACGCAGA TCATCATCAATGCCTAAAATTATTATGGTGGATGCGGGAGGGAAATGCTAAC AATTAAAGACCATAGAGGAAGGCAAAAGCACCTGTGCTGCCTGA [SEQ ID NO:21];
- (e) ATGTCTTCTGGAGGTCTTCTCCTGCTGGACTCCTCACCCCTCTGGGAGG TGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAATTCTGTAACTGCTTCC TGACACCAGGATCATGTAAGACTTACCGGAGCCTCCACTACAGCACACG TGATCGTGAATGCATAGAGTTATTATGGTGGATGCGGGAGGGAAATGCTAA CAATTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:23];
- (f) ATGTCTTCTGGAGGTCTTCTCCTGCTGGACTCCTCACCCCTCTGGGAGG TGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAAGTTCTGTAACTGCCTG CTGACATCGGACCATGGGATGACTTACCGGAGCCTCCACTACAGCCAC GTGAACATGAATGCATAGAGTTATTATGGTGGATGCAAAGGGAAATGCTA ACAACTTTAACCAAGAGCAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:25]; and
- (g) GGAGCTTCATCATGTTCTGGAGGTCTTCTCCTGCTGGACTCCTCAC CCTCTGGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCAGAGTTGTG TGAACATGCCTCCTGACACCGGACCATGTAGAGTCAGATCCCCATCCTTCTAC TACAACCCAGATGAACAAAAATGCCTAGAGTTATTATGGTGGATGCGAA GGGATGCTAACCAATTATCACCAAAGAGGAATGCGAAAGCACCTGTGC TGCCTGAATGAGGAGACCCCTCCTGGATTGGATCGACAGTTCCAACCTGACC CAAAGACCCCTGCTTCTGCCCTGGACCACCCCTGGACACCCCTCCCCAAACCC CACCCCTGGACTAATTCTTCTGCAATAAGCTTGGTTCCAGCT [SEQ ID NO:43]

46. (Original) A pharmaceutical composition for alleviating blood loss in a patient, said composition comprising the polypeptide of claim 8 and a pharmaceutically acceptable carrier.

47. (Withdrawn) A method for alleviating blood loss comprising the step of administering to a patient in need of such treatment a therapeutically effective dosage of the polypeptide of claim 8 in combination with a pharmaceutically acceptable carrier.

48. (Withdrawn) An anti-tumour agent comprising the polypeptide of claim 8 conjugated with an anti-fibrin antibody.

49. (New) The plasmin inhibitor of claim 1, further comprising the amino acid sequence ECESTCAA.

50. (New) The plasmin inhibitor of claim 1, further comprising the amino acid sequence NANNF.

51. (New) The plasmin inhibitor of claim 49, further comprising the amino acid sequence YGGC.

52. (New) The plasmin inhibitor of claim 1, which is conjugated to an anti-fibrin antibody.

53. (New) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 75% of the total material in the preparation is the plasmin inhibitor.

54. (New) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 90% of the total material in the preparation is the plasmin inhibitor.

55. (New) The plasmin inhibitor of claim 1, wherein "substantially pure" means that at least 95% of the total material in the preparation is the plasmin inhibitor.